REMARKS

Claims 1, 3-42 and 46-48 were pending in the application. Claims 1, 9 and 10 have been amended. Accordingly, claims 1, 3-42 and 46-48 will be remain pending in the application upon entry of the amendments presented herein.

Claim 1 was amended to remove a redundancy in the definition of the R_1-R_4 substituents. Claims 9 and 10 were amended to remove subject matter previously removed from claim 1, from which claims 9 and 10 depend. Support for the amendment of the claims can be found throughout the specification and claims as originally filed. In particular, support for the amendment of claims 9 and 10 can be found in the specification at least, for example, on page 7, line 29, and in claim 1, as amended; and claims 9 and 10, respectively, as previously amended. No new matter has been added.

Attached hereto as Appendix A is a marked-up version of the changes made to the specification and the claims by the current amendments. Appendix A is captioned **"Version with Markings to Show Changes Made."** Also attached hereto as Appendix B is a complete set of the claims that will be pending upon entry of the amendments presented herein.

Amendment of the claims is not to be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action or previous Office Actions, and was done solely to expedite prosecution of the instant application. Applicants hereby reserve the right to prosecute the claims as originally filed, or similar claims, in one or more continuation applications and/or divisional applications.

Claim Rejections - 35 U.S.C. §112

Rejection of Claims 1-42 and 46-48 under 35 U.S.C. §112, First Paragraph

The rejection of claims 1-42 and 46-48 under 35 U.S.C. §112, first paragraph, has been maintained for the reasons of record. The Office Action renews the allegation that the specification is only enabling for making and using 2-heptyl-3-hydroxy-4-quinolone, and that the specification otherwise lacks an enabling disclosure to make and use the invention commensurate in scope with the claims of the instant invention. Applicants respectfully traverse the rejection and reiterate herein the arguments presented in Applicants' response of January 9, 2003.

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The Office Action indicates that the starting materials and procedures for making the compounds of the instant invention other than 2-heptyl-3-hydroxy-4-quinolone (especially those compounds wherein R10-R24 are other than hydrogen, and wherein R2-4 are all halogen), "are not seen in the specification, ***but are required***." [Emphasis added.] Applicants disagree.

Applicants respectfully refer the Examiner to M.P.E.P. § 2164.08, which states that not everything necessary to practice the invention need be disclosed, and *what is well-known is best omitted.* Applicants submit that the starting materials and methods for making the claimed compounds are well-known in the art and, therefore, need not be disclosed in the application.

Indeed, the references of record, including those cited by the Examiner in the Office Action of September 9, 2002, establish that a substantial body of knowledge regarding the synthesis of quinolone derivatives was available to one of ordinary skill in the art at the time the instant application was filed. Although these derivatives are not encompassed by the claims of the invention, the references nevertheless provide examples of art that contributes to the substantial body of knowledge in the art of preparation of quinolone derivatives and the location/availability of starting materials. For example, the Examiner's attention is invited to the references cited in the previous office action that describe the synthesis of quinolone derivatives incorporating substituents on the quinolone ring (see for example, Guilhon *et al.*), as well as on the alkyl chain (see for example, Dekker *et al.*). One of ordinary skill in the art would have these references available for use in the preparation of the compounds of the invention (including compounds wherein R_{10}-R_{24} are other than hydrogen, and wherein R_2-R_4 are all halogen), eliminating the need for Applicants to disclose specifically the preparation of all of the possible compounds within the claimed genus. Thus, when the state of the art, as represented, for

example, by these references, is taken in combination with the teachings of the application and the specific example of the synthesis of 2-heptyl-3-hydroxy-4-quinolone described therein, there would be no question in the mind of the artisan of ordinary skill that the full scope of the claims is enabled.

Although the foregoing argument was made in Applicants' response of January 9, 2003, the Examiner did not specifically address the merits of the argument. Therefore, Applicants would appreciate the Examiner addressing this argument in the next office action.

The Office Action, on page 4, indicates that the use of quinolone compounds *as autoinducers* is "at an infancy stage". Whether or not this statement is true is irrelevant because claim 1 and the claims depending therefrom are directed to the compounds *per se*. In accordance with the invention, these compounds may be autoinducers, inhibitors or modulators as those terms are described in the instant application. The application also describes how to characterize the claimed compounds in accordance with these terms.

However, these terms are only an indication of the utility of the claimed compounds. For purposes of patentability, Applicants need only describe how to make and use the compounds and demonstrate one credible, substantial and real world utility. Applicants have done that and, therefore, are entitled to the claimed compounds, regardless of any other utilities the compounds may have, or of whether or not the use of the compounds for a particular purpose is "at any infancy stage".

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The Office Action also indicates that the autoinducer art in general provides support for the assertion that there is a high degree of unpredictability in the quinolone autoinducer art. The autoinducer art, and references cited as related thereto (including Bycroft), describe and detail ***homoserine lactone*** autoinducers ***only***. In particular, Bycroft discloses homoserine lactone autoinducer compounds and investigates the autoinducer activity of these compounds in terms of induction, *i.e.*, of luminescence. However, the compounds of Bycroft are ***homoserine lactones***, molecules having a core ring that is structurally distinct from the core ring of the ***quinolone*** compounds of the instant invention. Furthermore, Bycroft makes absolutely no reference to quinolone compounds or quinolone compounds as autoinducers. Therefore, assuming, *arguendo*, that the Bycroft reference demonstrates the unpredictability of homoserine lactone compounds, the determination in regard to the structural changes on the activities of the

compounds disclosed in Bycroft is not dispositive of the predictability/unpredictability of the changes in activity of the compounds of the instant invention upon similar structural changes.

No quinolone art has been cited to support the assertion that the art of ***quinolone*** autoinducers is highly unpredictable. Applicants submit that the alleged high degree of unpredictability in the homoserine lactone autoinducer art is not dispositive of the alleged unpredictability of quinolone autoinducers. Without more, Applicants are entitled to the presumption of correctness and operativeness by the PTO, and the only relevant concern of the PTO under the circumstances should concern the truth of the assertions contained in the application. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1967); see also, *In re Bowen*, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Office Action provides no evidence or relevant art that controverts the assertions made in the instant application.

Applicants also note there is an apparent contradiction in the rationale of the Office Action regarding the alleged unpredictability of the quinolone autoinducer art. On the one hand, the Office Action, on page 4, indicates that "[i]ndeed, 2-heptyl-3-hydroxy-4-quinolone, as a cell-to-signaling molecule (PQS) has only been identified ***a few years ago***. The art is therefore at an infancy stage." [Emphasis added.] On the other hand, the Office Action cites the body of homoserine lactone autoinducer art that has developed ***over more than 10 years*** to support the presumption of unpredictability the quinolone autoinducer art. Aside from the fact that the alleged unpredictability in the homoserine lactone autoinducer art is not dispositive of the alleged unpredictability of quinolone autoinducers, Applicants submit that there cannot be a high degree of unpredictability in an art that is "at an infancy stage" because there is an insufficient body of literature in the quinolone autoinducer art to establish any degree of unpredictability.

The Office Action also refers to two compounds (described in the instant application on page 24), not within the scope of the claims, as further support for the presumption of a high degree of unpredictability in that these two compounds did not show autoinducer activity similar to that of 2-heptyl-3-hydroxy-4-quinolone. Applicants respectfully remind the Examiner that the claims of the instant invention are directed to ***compounds***, which in turn may have a range of activities, *e.g.*, modulating (both enhancement and inhibition) of the activity of LasR and/or RhlR proteins and quinolone autoinducer compounds (*e.g.*, 2-heptyl-3-hydroxy-4-quinolone), as well as, though not necessarily, autoinducer activity (*e.g.*, 2-heptyl-3-hydroxy-4-quinolone). The fact that these two compounds did not demonstrate autoinducer activity does not mean that the compounds are not active as modulators (*e.g.*, inhibitors of the autoinducer activity of 2-heptyl-3-hydroxy-4-quinolone). In fact, at page 25, lines 1-2 of the application, Applicants indicate that "these two analogs were not tested in a competitive assay to determine that the

analogs did not bind to the PQS". Applicants clearly did not foreclose the possibility that these two compounds could have modulatory activity. Therefore, these two compounds do not demonstrate the general unpredictability in the art that the Office Action asserts, and do not make up for the deficiency of Bycroft in providing support for the statement that there is a high degree of unpredictability in the PQS autoinducer art.

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The Office Action on page 5 states that

> In the instant case, an example for a compound that 'modulates' the activity of PQS, either enhances or inhibits the autoinducer activity of PQS, 'modulates' or antagonizes the activity of Las R and/or the RhlR proteins as recited in the instant claims 29-34 has not been described in the specification....[and] undue experimentation would be required for one of ordinary skill in the art to use these compounds as claimed...where a high degree of unpredictability exists.

Applicants respectfully disagree.

Applicants have already addressed the issue of unpredictability. Moreover, the specification as originally filed describes a PQS bioassay, that was used to examine at least two other compounds (*i.e.*, a demonstration of the utility of this assay). The type of activity that a compound of the invention possesses can be easily determined by one of ordinary skill in the art using known methods (*see, e.g.*, U.S. Patent Nos. 5,591,872 and 6,057,288, and in published PCT international patent application Nos. WO 98/57618, WO 98/58075, WO 99/65889, and WO 00/06177) and those described in the instant specification (*e.g.*, the PQS assay described on pages 19-23 and in Example 1 on page 28) without undue experimentation.

In particular, the skilled artisan would readily appreciate that modulators of the autoinducer activity of 2-heptyl-3-hydroxy-4-quinolone could be determined without undue experimentation by adding the putative modulator (a compound within the scope of claim 1) to the bioassay for the PQS as described on page 28 (Example 1), and determining the result of such addition on the autoinducer activity of 2-heptyly-3-hydroxy-4-quinolone by measuring changes in the β-gal readout.

In regard to claims 32-34, the LasR and RhlR proteins are the putative autoinducer transcriptional regulator proteins as described in the Background section of the specification on page 2 lines 33-34. Therefore, it would be clear to one of ordinary skill in the art that modulators of the LasR and/or RhlR proteins could be determined by measuring the affect of the addition of quorum signaling molecules associated with the activity of these proteins; *i.e.*, modulators of LasR would affect the response to exogenously added N-(3-oxododecanoyl) homoserine lactone, while the modulators of RhlR would affect the response to exogenously added N-butyryl homoserine lactone. Support for this assertion is set forth in the application on page 2, lines 33-39 and pages 19-21, in the section of the specification entitled "Discovery of a Novel Cell-to-Cell Signal".

It appears that Office Action insists that there is a greater burden for disclosure in this case, based on the presumption of a "high degree of unpredictability in the autoinducer art." However, as discussed above, the Examiner has failed to prove that, in fact, there *is* a high degree of unpredictability in the **quinolone autoinducer art**.

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In view of the foregoing, Applicants submit that the claims 1-42 and 46-48 are fully enabled by the specification, and respectfully reconsideration and withdrawal of the rejection of these claims under §112, first paragraph.

Claim Rejections - 35 U.S.C. §102

Rejection of Claims 1, 4, 10-14, 19-28 32-42, 46-48 under 35 U.S.C. §102(b)

Claims 1, 2, 4, 10-14, 19-28 32-42, 46-48 were rejected under 35 U.S.C. §102(b) as anticipated by Takeda (Hakko Kogaku Zasshi (1959), 37, 59-63, abstract). The Office Action asserts that Takeda discloses the isolation of 2-heptyl-3-hydroxy-4-quinolone from a culture of *Pseudomonas aeruginosa*. Applicants respectfully traverse this rejection

Applicants respectfully point out that the substance isolated by Takeda, *i.e.*, substance B-A, was merely ***suggested*** to be 2-heptyl-3-hydroxy-4-quinolone. Moreover, Takeda makes this suggestion based solely on a melting point (typically only an indication of purity) and an ultraviolet absorption spectrum, which is far from what could be considered by the ordinarily skilled artisan as conclusive evidence of structure. Additionally, the Abstract indicates that the substance B-A isolated by Takeda ***possesses antibacterial action on gram-positive bacteria*** (the summary of data shown in Table 2).

In contrast, Applicants conclusively identified 2-heptyl-3-hydroxy-4-quinolone ("PQS," Pseudomonas Quinolone Signal) in the instant application using well-known techniques such as nuclear magnetic resonance, high performance liquid chromatography, and low and high resolution mass spectrometric analysis (see, for example, Figures 4 and 5 on page 23 of the specification, as well as Examples 2 and 4). In addition, 2-heptyl-3-hydroxy-4-quinolone was synthetically prepared as confirmation of the identity of the biologically isolated compound. Moreover, on page 27, lines 3-5 of the instant specification, it is noted that

> **PQS does not have detectable anti-*Staphylococcus aureus* or anti—*E. coli* activity**. However, this molecule showed activity as an intercellular signal that induced the *P. aeruginosa* virulence gene *las* B. (emphasis added)

Staphylococcus aureus is a gram-positive bacterium. Upon the conclusive identification of PQS, Applicants determined that the PQS compound **does not** have detectable anti-*Staphylococcus aureus* activity, in stark contrast to what is disclosed in the Takeda Abstract.

The possibility exists that *either* Takeda had more advanced analytical techniques that would render detectable that which the instant Applicants could not detect forty-one years later, *or* that the compound isolated by Takeda was not 2-heptyl-3-hydroxy-4-quinolone. As there can be no doubt that the state of the art on August 31, 2000 (the priority date for this application) was far superior to the state of the art in 1959 of detection of biological activity, the compound isolated by Takeda could not have been 2-heptyl-3-hydroxy-4-quinolone. Applicants note that the mere naming of a compound is not enough to establish anticipation. The reference must describe and enable the compound. *See, e.g., In re Schoenwald*, 22 USPQ 2d 1671 (Fed. Cir. 1992). Clearly, Takeda has failed to describe and enable 2-heptyl-3-hydroxy-4-quinolone.

The Office Action further indicates that although Takeda is silent on the various biological activities recited in the instant claims, these properties would be inherent in the prior art compound. To establish inherency, the missing properties must necessarily be present in the compound described and the existence of those properties must be appreciated by one of ordinary skill in the art. However, inherency cannot be established by probabilities or possibilities. *In re Robertson*, 49 USPQ2d 1949 (Fed. Cir. 1999). Applicants assert that ***Takeda did not isolate 2-heptyl-3-hydroxy-4-quinolone***, but rather substance B-A, another compound that has anti-bacterial activity against gram-positive bacteria.

As noted above, Applicants have shown that 2-heptyl-3-hydroxy-4-quinolone, an autoinducer, has no measurable anti-bacterial activity against gram positive bacteria. This is

consistent with the definition of an autoinducer – a compound that regulates the production of virulence factors.

Therefore, it is not possible for Takeda to have inherently disclosed the biological activities recited in the instant claims because Takeda did not isolate 2-heptyl-3-hydroxy-4-quinolone. In particular, the biological properties of the compounds of the instant application could not have been inherently disclosed by Takeda because the one biological property disclosed for Takeda's substance B-A (anti-bacterial activity against gram-positive bacteria) is in fact different from that of 2-heptyl-3-hydroxy-4-quinolone. In light of this, it cannot be said that the missing properties are necessarily present in the Takeda compound and the existence of those properties would be appreciated by one of ordinary skill in the art.

Furthermore, the pharmaceutical composition claims 35-40, the method of inhibiting infectivity of *Pseudomonas aeruginosa* claims 41-42, and the culture medium claims 46-48 are novel in light of Takeda, as Takeda does not teach or suggest the claimed methods, culture medium or pharmaceutical compositions of the vaguely identified substance B-A.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) of claims 1, 4, 10-14, 19-28 32-42, 46-48, or at a minimum, claims 35-42 and 46-48.

Claim Rejections - 35 U.S.C. §112

Rejection of Claims 9 and 10 under 35 U.S.C. §112, Second Paragraph

Claims 9 and 10 have been rejected under 35 U.S.C. §112, second paragraph. In particular, the Office Action states on page 6 that claims 9 and 10 contain subject matter that has no antecedent basis in claim 1. In this regard, Applicants have amended claims 9 and 10, and therefore respectfully request that this rejection be withdrawn.

SUMMARY

In view of the foregoing, entry of the amendments and remarks presented herein, reconsideration and withdrawal of all the objections and rejections, and allowance of the application with all pending claims are respectfully requested. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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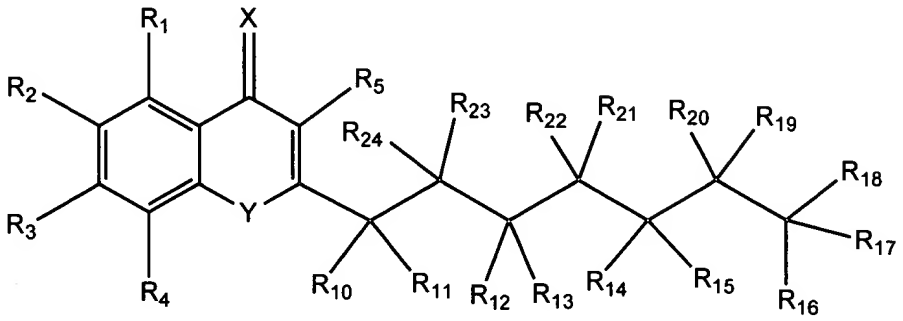
APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims

1. (Twice Amended) A compound of formula I

wherein:

(I) 

R_1-R_4 are independently H, alkyl, alkenyl, alkynyl, OH, NH_2, SH, O-R_6, N-R_7R_8, or a halogen;

R_5 is SH, OH, O-R_6, or N-R_7R_8;

R_6 is [H or] C_1-C_4 alkyl;

R_7 and R_8 are independently H, C_1-C_4 alkyl, O, or S;

X is S, O, or N-R_9;

Y is N-R_9;

R_9 is H, O, S, or C_1-C_4 alkyl;

R_{10}-R_{13} are independently H, C_1-C_4 alkyl, OH, NH_2, SH, O-R_{25}, N-$R_{26}R_{27}$, or a halogen, or R_{10} and R_{11} taken together form a carbonyl, a sulfonyl or an imino moiety, or R_{12} and R_{13} taken together form a carbonyl, a sulfonyl or an imino moiety;

R_{14}-R_{24} are independently H, C_1-C_4 alkyl, OH, NH_2, SH, O-R_{25}, N-$R_{26}R_{27}$, or a halogen;

R_{25} is H or C_1-C_4 alkyl; and

R_{26} and R_{27} are independently H, C_1-C_4 alkyl, O, or S; and

salts thereof.

9. The compound of claim 1, wherein Y is [O, S, or] N-R_9 and wherein R_9 is C_1-C_4 -alkyl.

10. The compound of claim 1, wherein R_5 is [H,] SH, O-R_6, or N-R_7R_8, and wherein R_6 is C_1-C_4 alkyl.